Studying arrhythmogenic right ventricular dysplasia with patient-specific iPSCs.

Journal: Nature

Publication Year: 2013

Authors: Changsung Kim, Johnson Wong, Jianyan Wen, Shirong Wang, Cheng Wang, Sean Spiering, Natalia G Kan, Sonia Forcales, Pier Lorenzo Puri, Teresa C Leone, Joseph E Marine, Hugh Calkins, Daniel P Kelly, Daniel P Judge, Huei-Sheng Vincent Chen

PubMed link: 23354045

Funding Grants: Development of Neuro-Coupled Human Embryonic Stem Cell-Derived Cardiac Pacemaker Cells., Endothelial cells and ion channel maturation of human stem cell-derived cardiomyocytes, Studying Arrhythmogenic Right Ventricular Dysplasia with patient-specific iPS cells

Public Summary:
Most heart conditions leading to sudden death or impaired cardiac pumping functions in the young people (<35 years old) are the results of genetic mutations inherited from parents. It is very difficult to find curative therapy for these inherited heart diseases due to late diagnosis and lack of understanding in how genetic mutations cause these diseases. One of these inherited heart diseases is named arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C). The specific disease features of ARVD/C are progressive heart muscle loss and their replacement by fat and scare tissues, which can lead to lethal irregular heart rhythms. We have made a significant breakthrough and successfully modeled ARVD/C within a few months in cell cultures using versatile stem cells derived from ARVD/C patients' skin cells with genetic mutations in cell-cell junctional proteins. These disease-specific stem cells can give rise to heart cells, which allow us to discover specific abnormalities in heart energy consumption of ARVD/C hearts that causes dysfunction and death of these diseased heart cells. Our study is the first to demonstrate that induction of adult-like energy metabolism has a critical role in establishing an adult-onset disease model using patient-specific stem cells. Using this model, we revealed crucial pathogenic insights that metabolic derangement in adult-like metabolic milieu underlies ARVD/C pathologies. Currently, there is no disease-slowing therapy to these inherited heart diseases except implanting a shocking device to prevent sudden death. With our newly-established ARVD/C patient-specific stem cell lines, we have elucidated novel disease-causing mechanisms and started developing novel disease-modifying therapeutic strategies.

Scientific Abstract:
Cellular reprogramming of somatic cells to patient-specific induced pluripotent stem cells (iPSCs) enables in vitro modelling of human genetic disorders for pathogenic investigations and therapeutic screens. However, using iPSC-derived cardiomyocytes (iPSC-CMs) to model an adult-onset heart disease remains challenging owing to the uncertainty regarding the ability of relatively immature iPSC-CMs to fully recapitulate adult disease phenotypes. Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) is an inherited heart disease characterized by pathological fatty infiltration and cardiomyocyte loss predominantly in the right ventricle, which is associated with life-threatening ventricular arrhythmias. Over 50% of affected individuals have desmosome gene mutations, most commonly in PKP2, encoding plakophilin-2 (ref. 9). The median age at presentation of ARVD/C is 26 years. We used previously published methods to generate iPSC lines from fibroblasts of two patients with ARVD/C and PKP2 mutations. Mutant PKP2 iPSC-CMs demonstrate abnormal plakoglobin nuclear translocation and decreased beta-catenin activity in cardiogenic conditions; yet, these abnormal features are insufficient to reproduce the pathological phenotypes of ARVD/C in standard cardiogenic conditions. Here we show that induction of adult-like metabolic energetics from an embryonic/glycolytic state and abnormal peroxisome proliferator-activated receptor gamma (PPAR-gamma) activation underlie the pathogenesis of ARVD/C. By co-activating normal PPAR-alpha-dependent metabolism and abnormal PPAR-gamma pathway in beating embryoid bodies (EBs) with defined media, we established an efficient ARVD/C in vitro model within 2 months. This model manifests exaggerated lipogenesis and apoptosis in mutant PKP2 iPSC-CMs. iPSC-CMs with a homozygous PKP2 mutation also had calcium-handling deficits. Our study is the first to demonstrate that induction of adult-like metabolism has a critical role in establishing an adult-onset disease model using patient-specific iPSCs. Using this model, we revealed crucial pathogenic insights that metabolic derangement in adult-like metabolic milieu underlies ARVD/C pathologies, enabling us to propose novel disease-modifying therapeutic strategies.

Source URL: https://www.cirm.ca.gov/about-cirm/publications/studying-arrhythmogenic-right-ventricular-dysplasia-patient-specific-ipscs